lower costs means accessing the databases of 602 of their 3,750 hospitals with a majority lacking a robust Enhanced Recovery After Surgery service, that too, could skew the results.

A better study would be a randomized, double-blinded one in which the only variable would be the use of IV acetaminophen *versus* oral acetaminophen for 24 h in a cohort of patients that did not include chronic opiate users and in which the multimodal regimen was standardized rather than determined by individual predilections. Ultimately, anesthesiologists typically have limited control over pain management of patients and infrequently beyond the first postoperative day. It is impossible to create a major impact on an inflammatory process that will extend well beyond the first 24 h.[4] Consequently, until we have complete ownership of perioperative pain management well beyond the immediate postoperative period using all available modalities, we will have minimal impact, IV acetaminophen or not.

Competing Interests

The author declares no competing interests.

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When Large Administrative Databases Provide Less Relevant Information than Randomized Studies

To the Editor:

We read with interest the retrospective study conducted by Wasserman *et al.*,[1] based on a national administrative database assessing the impact of intravenous acetaminophen on perioperative opioid utilization and outcomes in patients undergoing open colectomies.

Research based on administrative data sets can provide information of major importance for clinical practice, but the interpretation of results is difficult, and causal inference is circumscribed by intrinsic methodologic limitations. In this study,[1] we observed three main limitations with potential impact on result interpretation: (1) the validity of main outcome data (morphine consumption) is questionable compared with monitored clinical studies, (2) the doses of acetaminophen administered in the treated group were heterogeneous, and (3) the estimation of treatment effect is likely to be biased by uncontrolled confounding factors. The sensitivity analysis provided by the authors is not enough to provide an unbiased estimation of treatment effect. To minimize bias, a propensity score analysis[2] or another sophisticated multivariable matching process[3] should have been performed, because the patients who received acetaminophen differed markedly from those who did not. Despite the large sample size (n = 181,640),[1] we believe that the average treatment effect estimation is not robust enough to support any practice recommendations based on this study. Therefore, the amount of new information is relatively limited.

Although we thank the authors for not stating recommendations based on their results, we respectfully disagree with their conclusions: "Important next steps include validation of these results with alternative data and identifying patients and administration schedules (*e.g.*, routine IV acetaminophen every 6 h, dosing for 48 h) most likely to result in benefit."[1] The largest randomized control trial (n = 550 patients) evaluating the treatment effect of a homogeneous and appropriate dose of acetaminophen demonstrated a reduction in morphine requirements greater than the threshold prespecified by Wasserman *et al.*[1] (−31%; $P < 0.001$) and was not cited.[4] Citing appropriate references allows readers to understand new results and interpret them while taking into account results obtained using a high level of evidence-based studies. Such an approach in the

reporting research would limit the frequent claims for more and bigger studies, when results are already available in the literature.

Large administrative databases provide a vast amount of data reflecting our clinical practice. However, only powered, randomized, controlled trials provide unbiased estimation of treatment effect. In this clinical setting (*i.e.*, impact of intravenous acetaminophen on postoperative requirements), we do not believe that additional observational cohort analyses or additional randomized studies or meta-analyses[5] are a priority, because we already have the response.[4]

Last, although Wasserman *et al.*[1] also studied the incidence of outcome (*i.e.*, opioid-related adverse effect) and not only morphine consumption, we still consider that opioid consumption is definitely not a clinically relevant primary endpoint and could not be an intermediate outcome of a patient-related optimal one.[4] Taking into account the lack of demonstrated effect of acetaminophen on opioid-related adverse effect, this drug probably has minimal clinically relevant effects in the early perioperative period.

Competing Interests

The authors declare no competing interests.

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In Reply:

We welcome the thoughtful comments by Dr. Steadman and Riou *et al.*, in reply to our study.[1] We aimed to evaluate the use of IV acetaminophen and its association with outcomes including opioid utilization, opioid-related adverse effects, and cost and length of hospitalization. Dr. Steadman mentioned several limitations of our study—some justified (and mentioned in our study's Limitations section) and some less so—and observational research in general. Dr. Steadman states that "A better study would be a randomized double-blinded one in which the only variable would be the use of IV acetaminophen *versus* oral acetaminophen for 24 h in a cohort of patients that did not include chronic opiate users, and in which the multimodal regimen was standardized rather than determined by individual predilections." We agree that this would be an ideal study situation to a certain extent. However, such a study would be difficult to conduct or would significantly lack generalizability, because common practice almost never is in alignment with the control group or intervention group. Indeed, multiple (nonopioid) modalities (*e.g.*, nerve blocks, neuraxial analgesia, acetaminophen, and gabapentinoids, among others) are available for use in multimodal regimens; this results in an exponential increase in the number of potential combinations to use in practice.[2] Therefore, there currently is no universally recognized standard regimen to be used in a trial desirous of generalizability, and identifying the optimal multimodal regimen in a trial setting would be impossible given the sheer number of combinations. A more practical approach would be to use observational data to identify combinations of nonopioid modalities and timing that may result in the most optimal outcomes. This will inform trials where a selected number of multimodal regimens may be compared. Particularly the "individual predilections" noted emphasizes the difference between trial and real-world settings that provided the most thought-provoking result from our study: IV acetaminophen is mostly used as a single-dose administration on the day of surgery, which is not likely to result in a clinically relevant reduction of opioid utilization. Indeed, real-world use of drugs often differs from use in controlled trial settings where they are deemed efficacious.[3] We maintain that the value of this investigation is the demonstration of the real-world use of IV acetaminophen that was not associated with clinically significant reductions in opioid utilization. Importantly, we agree with Dr. Steadman that "Giving a single dose of IV acetaminophen and expecting a miraculous